The adult livers of immunodeficient mice support human hematopoiesis: evidence for a hepatic mast cell population that develops early in human ontogeny.

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Public Summary:
The livers of special mice (which lack the ability to fight off foreign substances) are able to produce human blood cells, thus providing a way to study adult human liver blood formation. Our study is also the first clear demonstration of mast cells being present in the human fetus.

Scientific Abstract:
The liver plays a vital role in hematopoiesis during mammalian prenatal development but its hematopoietic output declines during the perinatal period. Nonetheless, hepatic hematopoiesis is believed to persist into adulthood. We sought to model human adult-liver hematopoiesis by transplantation of fetal and neonatal hematopoietic stem cells (HSCs) into adult immunodeficient mice. Livers were found to be engrafted with human cells consisting primarily of monocytes and B-cells with lesser contributions by erythrocytes, T-cells, NK-cells and mast-cells. A resident population of CD117(++)CD203c(+) mast cells was also documented in human midgestation liver, indicating that these cells comprise part of the liver's resident immune cell repertoire throughout human ontogeny. The murine liver was shown to support human multilineage hematopoiesis up to 321 days after transplant. Evidence of murine hepatic hematopoiesis was also found in common mouse strains as old as 2 years. Human HSC engraftment of the murine liver was demonstrated by detection of high proliferative-potential colony-forming cells in clonal cultures, observation of CD38-CD34(++) and CD133(+)CD34(++) cells by flow cytometry, and hematopoietic reconstitution of secondary transplant recipients of chimeric liver cells. Additionally, chimeric mice with both hematopoietic and endothelial reconstitution were generated by intrasplenic injection of immunodeficient mice with liver specific expression of the urokinase-type plasminogen activator (uPA) transgene. In conclusion, the murine liver is shown to be a hematopoietic organ throughout adult life that can also support human hematopoiesis in severely immunodeficient strains. Further humanization of the murine liver can be achieved in mice harboring an uPA transgene, which support engraftment of non-hematopoietic cells types. Thus, offering a model system to study the interaction of diverse human liver cell types that regulate hematopoiesis and immune function in the liver.